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Determinants of Micro-embolic Signals in Patients with Atherosclerotic Plaques of the Internal Carotid Artery

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Abstract *Background and purpose:* This study aimed to investigate the embolic potential of carotid plaques, employing both the presence and the rate of micro-embolic signals (MESs), based on the presence and timing (current or past) of symptoms, degree of stenosis and ultrasonic characteristics of plaques.
Methods: We used the transcranial Doppler (TCD) to monitor MES and the Doppler ultrasound to classify carotid plaques in newly symptomatic (acute stroke or transient ischaemic attack (TIA)), formerly symptomatic (relevant stroke or TIA per anamnesis) and asymptomatic patients with internal carotid artery (ICA) stenosis.
Results: Stroke-related arteries evidenced a significantly greater presence of MES than the TIA-related and asymptomatic arteries ($p = 0.04$), with no significant difference found between the latter two groups (stroke: 42/90, 46.7%; TIA: 15/49, 30.6%; asymptomatic: 40/130, 30.8%). Adjustment for anti-platelet treatment did not change this finding. The degree of stenosis, ultrasonic characteristics of texture and the density of plaques were not found to be associated with the presence or quantity of MES.
Conclusion: MESs are present significantly more often in stenosed, stroke-related carotid arteries as compared with TIA-related or asymptomatic arteries. Neither the ultrasonic characteristics nor the degree of stenosis were found to influence the presence or rate of MES.

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Different aspects of monitoring of micro-embolic signals (MESs) in patients with atherosclerotic disease of the internal carotid artery (ICA) are reflected in the literature. Despite the increasing degree of research attention

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devoted to this problem, controversies still remain about which factors determine the presence and rate of MES. This study aimed to investigate different factors which may influence both the presence and the rate of MES in patients with ICA atherosclerotic disease. Specifically, the presence (symptomatic vs. asymptomatic) and timing (current or past) of symptoms, the degree of stenosis and the ultrasonic characteristics of the plaques were examined.

Patients and Methods

Patients

The study cohort consisted of all patients suffering from carotid stenosis who underwent transcranial Doppler (TCD) examination, MES monitoring and cervical duplex at the Rambam Health Care Campus in Haifa, Israel. Data were prospectively collected for a total of 229 patients, including 110 patients from the department of neurology, 74 patients from the department of vascular surgery and 45 patients from the department of invasive cardiology. A total of 269 arteries, in which duplex showed carotid plaques, were included in the final analysis.

With regard to the degree of stenosis, duplex revealed 64 arteries with mild (less than 50%) stenosis of the ICA, 56 arteries with moderate (50–69%) stenosis and 149 arteries with severe (70–99%) stenosis. As for the presence and timing of symptoms, there were 130 asymptomatic arteries – 39 formerly symptomatic (transient ischaemic attack (TIA) or stroke in the past, including 26 TIA- and 13 stroke-related arteries; time range from index event 5–91 months) – and 100 newly symptomatic arteries (23 TIA- and 77 stroke-related, examined during the first 96 h after admission). Because patients could have both a symptomatic and an asymptomatic artery, neither a simple categorisation of patients as 'symptomatic' or 'asymptomatic' nor a corresponding grouping by demographic characteristics and risk factors was possible.

MES monitoring

MES monitoring by TCD (Pioneer TC 8080, Nicolett Vyasys, USA) was performed at the level of the middle cerebral artery (MCA) on the side of the carotid stenosis (detected previously by cervical duplex) through the temporal window by an operator (E.K.). The duration of monitoring was 30 min, and the parameters used for the monitoring have been described earlier.[1] A threshold of 6 dB was chosen for embolus detection. The depth of insonation was 48–65 mm for MCA stem visualisation; monitoring was done at the depth which displayed the best flow signal. Single-gate mode was used for monitoring. Detection of the MES was based on the differences between MES and blood-flow intensities, in accordance with accepted criteria.[2] We used an automatic embolus detection system, but MESs were re-examined by one of the authors (E.K) off-line afterwards, and those MESs which were recognised as artefacts were rejected.

Cervical duplex and plaque analysis

A single operator (E.K.) performed all duplex ultrasound (DU) examinations with a 4–8 linear array probe by using the HD 11 Philips Ultrasound system (The Netherlands). The common carotid artery, ICA, carotid bifurcation and external carotid artery were examined by B-mode and colour-flow modalities. The maximal peak systolic velocity (PSV) and end-diastolic velocity (EDV) were recorded from each location. The grading of severe carotid stenosis was calculated according to an international consensus.[3] According to the results of the B-mode imaging, the types of plaques were marked as either homogeneous or heterogeneous. In turn, the homogeneous plaques were defined as isoechoic, hypoechoic or hyperechoic.[4,5]

Density of plaques

The B-mode settings were adjusted to obtain a clear image of the vessel lumen as well as of the echo-dense area of the adventitia close to the plaque. Images were stored on a compact disc (CD) and then standardised on a personal computer. Adobe Photoshop 7.0 (Adobe Systems, San Jose, CA, USA) was used to calculate the density of plaques by grey-scale median (GSM) scores, as previously described in the literature.[6]

Statistics

Statistical analysis consisted of chi-square and analysis of variance (ANOVA) for categorical and continuous outcome variables, respectively. A multivariate logistic regression model for the presence of MES using age, sex, hypertension, diabetes, hyperlipidaemia, smoking, atrial fibrillation (AF), symptomaticity (TIA, stroke, asymptomatic, etc.), texture characteristics, plaque density and severity of stenosis was tested. In order to control for the effects of anti-platelet treatment, separate logistic regression analyses were also conducted. Both JMP and Statistical Analysis Software (SAS, SAS Institute, Cary, NC, USA) were used for the statistical analyses.

Results

The patients' age ranged from 28 to 93 years, with a median of 68 years. There were 178 male and 51 female patients. The distribution of the main vascular risk factors for the whole group is presented in Table 1. Table 2 presents the distribution of anti-platelets and statin treatments in different patient groups. All analyses and correlations were performed for plaque-bearing arteries and not for patients. Actual results of the MES monitoring (by arteries) are presented in Table 3.

Table 1 Distribution of vascular risk factors in patients included into the study

Risk factor	Number (percentage)
Hypertension	183 (80%)
Diabetes	83 (36%)
Hyperlipidaemia	164 (72%)
Smoking	100 (43%)
Ischaemic heart disease	111 (48%)
Atrial fibrillation	12 (5%)

Table 2 Details of treatment in different groups of patients

Treatment/ category of patients	Aspirin	Clopidogrel	Aspirin + Clopidogrel	Statins
TIA	34 (73.9%)	1 (2.2%)	6 (13%)	32 (69.6%)
Stroke	39 (50.7%)	8 (10.4%)	4 (5.2%)	38 (49.4%)
Asymptomatic	57 (54.8%)	5 (4.8%)	21 (20.2%)	70 (67.3%)

MES and symptomaticity

When we compared all stroke-related, TIA-related and asymptomatic arteries, the stroke-related arteries evidenced a significantly greater presence of MES (as evaluated by on/off criteria) than the other two groups ($p = 0.04$), with no differences found between the asymptomatic and the TIA-related arteries (stroke-related arteries: 42/90, 46.7%; asymptomatic-related arteries: 40/130, 30.8%; TIA-related arteries: 15/49, 30.6%). No differences were found between newly symptomatic and formerly symptomatic arteries, either including or excluding those that were TIA-related. A multivariate logistic regression model for the presence of MES using age, sex, hypertension, diabetes, hyperlipidaemia, smoking, AF, symptomaticity (TIA, stroke, asymptomatic, etc.), texture characteristics, plaque density and severity of stenosis was not significant.

We also performed an adjustment based on treatment with anti-platelets, including both symptomaticity and treatment, using logistic regression models for the presence of MES. The results showed that significant differences between asymptomatic and stroke-related arteries were still present ($p = 0.03$).

When the relationship between symptomaticity and the number of MES was examined, no differences were found between the groups when the TIA- and the stroke-related arteries were considered as a single symptomatic group (asymptomatic-related arteries: 1.2 ± 0.2; symptomatic-related, including TIA-related: 2.0 ± 0.5; NS). However, when we removed the TIA-related arteries from the analyses, we found a significant difference in the mean rate of MES in the stroke-related arteries as compared with the asymptomatic-related arteries (stroke-related: 1.7 ± 0.5; asymptomatic-related: 0.8 ± 0.2; $p = 0.04$).

MES and severity of stenosis

The severity of stenosis was not associated with the presence of MES (arteries with mild stenosis: 25/64, 39.1%; arteries with moderate stenosis: 18/56, 32.1%; arteries with severe stenosis: 54/149, 36.2%; NS). Moreover, severity had no influence on the number of MESs (mean $\pm$ standard error $-$ arteries with mild stenosis: 1.4 ± 0.6; arteries with moderate stenosis: 1.5 ± 0.6; arteries with severe stenosis: 0.8 ± 0.2; NS).

MES and texture of plaques

There was no influence of ultrasonic texture characteristics or plaque density on the presence of MES (see Table 4). The texture of plaques also had no influence on the number of MESs (mean $\pm$ standard error $-$ heterogeneous: 1.3 ± 0.3; homogeneous anechoic: 0.8 ± 0.3; homogeneous hyperechoic: 1.3 ± 0.7; homogeneous isoechoic: 0.7 ± 0.3; NS). Logistic regression adjustment for anti-platelet treatment did not change any of the previous non-significant results related to the degree of stenosis or the ultrasonic characteristics. Finally, there was no correlation found between the density of plaques and the number of MESs ($r = 0.012$; NS).

Discussion

There are substantial data in the literature on different aspects of carotid stenosis influencing the presence and rate of MES. However, the results are mixed, and there are few comprehensive studies exploring all aspects of carotid disease as a complex problem in a representative cohort of patients. This study presents data on the influence of

Table 3 Actual results of MES monitoring (by arteries) depending on arteries' characteristics

Number of MES/artery and plaque characteristic	0	1	2	3	4	5	6—10	11—20	30—50	More than 50
Mild stenosis	39	14	3	3	—	—	2	1	1	1
Moderate stenosis	38	9	5	—	—	—	1	2	1	—
Severe stenosis	95	23	17	3	3	—	8	—	—	—
Asymptomatic-related	90	18	12	3	—	—	7	—	—	—
Stroke-related	46	24	8	2	1	—	2	2	2	
TIA-related	34	4	5	1	2	—	2	1	—	1
Heterogeneous	101	27	15	3	3	—	9	1	2	1
Homogeneous, anechoic	41	11	5	2	2	—	1	1	—	—
Homogeneous, hyperechoic	16	6	2	—	—	—	1	1	—	—
Homogeneous, isoechoic	14	1	3	1	1	—	—	—	—	—

Table 4 Ultrasonic characteristics of plaque texture and presence of MES

Texture of plaque	MES+	MES−	*p*
Heterogeneous	58, 36.48%	101, 63.52%	NS
Homogenous, Anechoic	22, 34.92%	41, 65.08%	NS
Homogenous, Hyperechoic	10, 38.46%	16, 61.54%	NS
Homogenous, Isoechoic	6, 30.00%	14, 70.00%	NS
Plaque density	79.0 ± 53.0	74.4 ± 51.1	NS

Note: Texture data for one artery (one patient) is missing from our database.

symptomaticity, the degree of carotid stenosis and the ultrasonic characteristics on the presence and rate of MES. The few studies in the literature on the interrelation between the ultrasonic texture of plaques and the presence of MES have yielded contradictory results. Mayor et al.,[7] showed that anechogenic/hypoechogenic plaques are associated with the presence of MES, whereas Sztajzel et al.,[8] revealed that a low mean GSM value of plaque is associated with MES. In the present study, we were unable to establish any association between qualitative (type of plaque) or quantitative (density of plaque) ultrasonic characteristics and the presence or rate of MES. This finding is in line with the results of another large study[9] on patients suffering from severe carotid stenosis.

The correlation between the degree of stenosis and MES has been previously studied, with somewhat controversial results and a clear understanding that factors other than the degree of stenosis are also important in determining high-risk carotid plaque.[10] Babikian and colleagues concluded that MESs are significantly more common distal to lesions, causing anywhere from 50% to more than 70% of ICA stenosis.[11,12] Orlandi et al.,[13] found that MESs were significantly more frequent in patients with a higher degree of carotid stenosis, and Droste et al.,[14] showed that both positivity for the presence and the number of MESs increased in relation to the rising degree of stenosis. Similar results were shown by Akiyama et al.,[15] Siebler et al.[16] and Gao et al.[17] The main limitation of all the above-mentioned studies, with the exception of one,[12] is the small number of patients and arteries studied. Our study did not reveal an association between the presence of MES and an increasing degree of carotid stenosis. Other studies also point to the absence of such dependence[18] or to insufficient statistical significance of relations between the degree of stenosis and the presence of MES.[19]

The most interesting and important aspect of MES monitoring in patients with carotid stenosis is the possible association between MES and the presence or absence of clinical manifestations. It seems well established that there is an association between the presence of symptoms and a greater rate of MES.[14,20–22] This finding was confirmed in the present study as well. However, there are two interesting points to be noted based on our results: first, contrary to Forteza et al.,[23] we found that TIA-related arteries were significantly less emboliogenic than stroke-related arteries; second, we did not find any differences in the presence or the rate of MES between new and former stroke-related arteries. This finding contradicts the well-established fact that the most emboliogenic period in the general stroke population is close to the acute stroke,[24] and can be partially explained by the small sample size of patients with stroke in the past. There are some limitations of our study. First, the ultrasonographer was not blinded to the clinical status of patients, though any possible bias would have been controlled by the automatic online embolus detection system used. Second, we were also unable to exclude the cardiac origin of emboli because TEE was not a part of the study protocol. Finally, the multivariate logistic regression model was not significant, perhaps due to the insufficient sample size.

In conclusion, we can summarise that stroke-related arteries (acute or in the past) are associated with a higher presence of MES, while there is no influence of the ultrasonic texture, density of plaques or degree of stenosis on the presence and the rate of MES.

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